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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/636,243	08/10/2000	Bryan S. Wang	8325-1004 (M4-US1)	6438
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ROBINS & PASTERNAK 1731 EMBARCADERO ROAD SUITE 230 PALO ALTO, CA 94303			WESSENDORF, TERESA D	
		ART UNIT	PAPER NUMBER	
		1639		
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/636,243	WANG ET AL.	
	Examiner	Art Unit	
	TERESA WESSENDORF	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 11 February 2009.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 5,6,20 and 21 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 5,6,20-21 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Status of Claims

Claims 5-6 and 20-21 (with respect to the elected species of 10-residue length) are pending and under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

As a preliminary matter, the inadvertent omission of claim 21 in the 35 USC rejection heading below is regretted. However, this claim was addressed and included in the response to applicants' arguments in the last Office action.

Claim Rejections - 35 USC § 103

Claims 5-6 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pomerantz in view of Krylov [or Marmostein] for the reasons of record as based on the Board's decision and reiterated below.

The Pomerantz publication has been described for its disclosure of a zinc finger fused to the naturally occurring dimerization domain extracted from the GAL4 protein. Pomerantz's fusion protein differs from the fusion protein contained in the zinc finger complex of claim 5 by having a naturally occurring dimerization domain, instead Pomerantz points the skilled artisan directly to prior art publications that teach modified dimerization domains. Such domains are non-naturally occurring

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and "join each other by specific binding," meeting the requirements of the claimed "peptide linkers." See claim 5. In particular, reference 19 (hereinafter "Krylov"), cited by Pomerantz for its studies of the coiled-coil interaction motif, describes "protein design rules that can be used to modify leucine zipper-containing proteins to possess novel dimerization properties." Krylov, page 2850, column 1. "33 different leucine zipper proteins containing 27 different systematic combinations of amino acids" were produced. Id., page 2856, column 2 ("Discussion"). See also Fig. IB for a list of exemplary "mutant proteins." Id., page 2850, column 2. The mutant proteins were mixed together under conditions which facilitated dimer formation. By measuring the stability of the dimers formed (id., page 2852-53, "Thermodynamic stability"), Krylov was able to demonstrate that certain modified dimers had increased stability and specificity as compared to the unmodified form. ("Novel heterologous interactions regulate dimerization specificity In the second mixing experiment, the stability of the heterodimer is calculated to be greater than the average of the two homodimer stabilities, thus favoring the formation of heterodimers." Id., page 2856, columns 1-2.) Thus, the element missing from Pomerantz - non-naturally occurring peptide linkers - is supplied by Krylov. The skilled worker would have had a

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reasonable expectation that Krylov's domains could be utilized to complex zinc fingers to which they are attached in view of Krylov's success in not only modifying their binding activity, but in making it stronger (i.e., more stable). Krylov also teaches dimerization domains having the same sequence, meeting the limitations of claim 6. See e.g., id., page 2856, column i, describing homo- and heterodimers, where the homodimers have "the same sequence." Pomerantz describes dimers between ZFGDI fusion protein, where each fusion contains the same zinc finger. Pomerantz, Abstract ("a dimeric zinc finger protein, ZFGDI"). This meets the requirements of claim 20. In sum, we find that Pomerantz and Krylov disclose all elements of the subject matter recited in claims 5, 6, and 20. For the reasons discussed above, the skilled worker would have considered these claims obvious in view of Pomerantz's express suggestion to combine its teaching with Krylov (i.e., reference 19), and Krylov's disclosure that would have led the skilled worker to reasonably expect that the combination would work.

Response to Arguments

Applicants state that for the reasons of record and reiterated herein, neither Pomerantz nor Krylov teach or suggest non-covalent linkage of 2 fusion proteins using two non-

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naturally occurring linker peptides less than 30 amino acids in length. Rather, Pomerantz and Krylov are cited for teaching much longer dimerization peptides that are either naturally occurring Gal4 domains of 59 amino acids in length or mutated leucine zipper-containing proteins of 80 amino acids in length. Thus, the rejection is premised on the assertion that references alleged disclosure that covalent linkage using a single peptide linker of 30 amino acids or less is somehow predictive of the claimed non-covalently molecules. However, the fact remains that the references and art as a whole teach that covalent peptide linkers are completely different than non-covalent dimerization peptides. Hence, there is no suggestion and nothing predictable about using short single peptides used for covalent linkage as dimerizing, non-covalent linkages.

In response, the examiner's responses to applicants' arguments of record are also incorporated herein. As stated in the last Office action, the art appreciates the use or teaches the conventionality of a short length peptide linker to link two proteins whether by covalent or non-covalent linking.

Applicants argue that Pomerantz clearly teaches that covalent linkage and non-covalent dimerization are completely different strategies (Pomerantz, page 966, left column, emphasis added):

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Dimer formation, frequently employed by natural DNA-binding proteins to enhance the affinity and specificity of recognition provides **another** attractive design strategy Design strategies that employ dimerization also may provide a useful **alternative to the covalent linkage of multiple DNA-binding domains.** Large covalent assemblies might have higher absolute affinity for nonspecific DNA sites and might become kinetically trapped at inappropriate sites in the genome. Dimerization provides an **alternative way** of bringing multiple domains together as a functional recognition unit.

Clearly, this is not in any way a suggestion to use the short covalent peptides for dimerization. Nor does it in any way establish that peptides of 30 amino acids or less were known by the skilled artisan to be predictably used as either covalent or non-covalent linkers.

In reply, the strategy for designing a short or long length linker is immaterial as the claim length does not recite for any strategy for dimer formation. The teachings of Pomerantz that one can use either one of the strategy for dimer formation would lead one having ordinary skill in the art (who are highly skilled, highly educated and sophisticated person) to the desired linkage.

Pomerantz teaches or at least suggests at e.g., paragraph bridging pages 965 and 966 the heterologous modules fused with short peptide linker using computer modeling. Such suggestion of a shorter linker than the Gal4 would lead one having ordinary skill in the art to the desirability of a shorter linker.

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Furthermore as Pomerantz discloses at page 966, second complete paragraph, the dimerization motif does not appear to require species sequences for binding. It would within the ordinary skill in the art to use a short linker to fuse two known zinc finger proteins. The prior art and the specification (page 15, line 16) disclose short linkers (5-12 residues) albeit, for covalent linkage. Whether the short linkers used to fuse two proteins are covalent or non-covalent linkage is immaterial as the prior art teaches or at least suggests the desirability of a short linker. As stated by applicants at paragraph bridging pages 3-4 of the (8/13/08) REMARKS (including the prior art cited therein):

Dimerization modules of the type reported here may be useful when designing new zinc finger proteins that recognize extended binding sites, **and such modules provide effective alternatives to covalent linkage (Liu et al., Proc. Natl. Acad. Sci. USA 94, 5525 (1997); Kim et al., Proc. Natl. Acad. Sci. USA 95, 2812 (1998)) or to the use of coiled-coil dimerization domains** (Pomerantz et al., Biochemistry 37, 965 (1998)). (Emphasis added).

Applicants argue that any teachings of the as-filed specification regarding the claimed short dimerizing peptides cannot be used against Applicants as this is clearly impermissible hindsight reconstruction based on Applicants' first showing that shorter, non-naturally occurring dimerizing peptides are indeed functional. The passages of the

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specification actually show that it was unpredictable to use shorter linkers for dimerization.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The cited section of the specification is not relied upon for its disclosure rather for the knowledge clearly present in the prior art as cited therein (underscored). The specification (e.g., page 36, lines 2-12) recites:

The success of the initial screen, which yielded several different peptides that mediate dimerization, suggests that such peptides are **relatively "common"** in sequence space. **Zhang et al. (19) have isolated dimerization elements by fusing 5 random fragments** of the yeast genome to the DNA-binding domain of lambda repressor and selecting fusion proteins that reconstitute repressor activity. **This group reached similar conclusions regarding the frequency of functional dimerization domains.** Our finding may help explain why dimerization elements are **so common** and have such diverse sequences in natural DNA-binding proteins. The peptide that we have isolated may be

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analogous - in an evolutionary and functional sense - to the peptide extensions that are responsible for heterodimerization of certain homeodomain proteins **(20-22)**. (Emphasis supplied).

Furthermore, the artisan working in this field is highly educated, sophisticated person. Generally they have at their disposal laboratory facilities e.g., computer (modeling) as taught or at least suggested by Pomerantz at e.g., paragraph bridging pages 965 and 966.

Applicants argue that for its part, Krylov is admittedly silent as to covalent linkages. In addition, Krylov fails to teach or suggest dimerizing proteins of 30 or fewer amino acids. The assertion that because Krylov teaches that the leucine zipper domain of the dimerization domain is made up of 4 heptad repeats does not in any way teach or suggest peptides as claimed. First, Krylov is clear that the leucine zipper domain of their protein is made up of 4 heptads and 3 amino acids N-terminal to the first heptad (ITI in Figure 1B) and at least 1 amino acid C-terminal to fourth heptad (I in Figure 1B). Indeed, the fourth heptad is actually octad as it contains a second g residue. (I in Figure 1B). Thus, Krylov teaches that the leucine zipper domain of VBP contains 32 amino acid residues, which does not fall within the scope of the claims.

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In reply, again applicants' arguments as to the covalent linkage are not commensurate in scope with the claims which do not recite the kind of linkage for the linker. Nevertheless, the suggested teaching so Krylov (e.g., page 2849, the abstract and paragraph bridging col. 1 and col. 2 suffice the finding of obviousness. Krylov describes a repeating helical dimerization interface... a repeating structural unit of two helical turns or **seven amino acids** (a heptad repeat) (reads on less than 30 amino acids of claim 5) of the leucine zipper domain made up of 4 heptads (or even an octad, as argued). There is nothing in the specification that demonstrates that the claim 30-residue peptide produces new and unexpected results from that of Krylov, 32-residue. As read in the light of the specification the chosen claim length of 30 or less is in the scope of "**the peptide size [can vary] from about 2-500 amino acids**, (pages 11, lines 20-21), including Krylov's 32-residue peptide length.

As held by the majority in Merck & Co. Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 10 USPQ 2d 1843 (Fed. Cir. 1989), at 10 USPQ 2d 1846:

That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition **is used for the identical purpose taught by the prior art**. See In re Corkill, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985)

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(obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among "thousands of compounds"); In re Susi, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellants generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives"). (Emphasis added).

There is nothing unpredictable in varying the size or length of a given linker, especially a peptide linker of such short length as claim, given the range already taught in the art. The court in KSR International Co. v. Teleflex Inc., 550 USPQ2d 1385 (2007) states:

When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions."

No claim is allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will

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expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA WESSENDORF whose telephone number is (571)272-0812. The examiner can normally be reached on flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TERESA WESSENDORF/
Primary Examiner, Art Unit 1639